CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES

https://cajmns.casjournal.org/index.php/CAJMNS

Volume: 07 Issue: 01 | January 2026 ISSN: 2660-4159

Article

Effect of Autologous Platelet-Rich Fibrin on Pedicle Skin Graft Healing in Goats: Clinical and Biochemical Evaluation

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Abstract: Objective: Avulsion injuries often require advanced reconstructive approaches such as pedicle skin grafting, yet graft survival and healing remain challenging. This study aimed to investigate the clinical and biochemical effects of autologous platelet-rich fibrin (PRF) on pedicle skin graft healing in goats **Materials and method**: Fifteen healthy female goats (7–8 months old, 18–20 kg) were subjected to bilateral standardized trunk wounds. Pedicle skin flaps (2×6 cm) were advanced over 2×2 cm defects and divided into two groups: control (without PRF) and PRF-treated. PRF was prepared by centrifugation of autologous blood samples and applied locally before wound closure. Clinical assessments (exudation, swelling, and graft appearance) were conducted postoperatively. Biochemical analysis included hydroxyproline content (days 7, 14, and 21) and wound surface pH (days 5, 7, 14, and 21). Data were analyzed using independent samples t-test ($p \leq 0.05$) **Results**: The PRF-treated group demonstrated a significantly faster resolution of swelling and higher exudation scores within the inflammatory phase, consistent with accelerated healing. Hydroxyproline levels were significantly elevated in PRF-treated grafts at days 7 and 14, indicating enhanced collagen synthesis, but returned to baseline by day 21. pH analysis revealed significantly higher alkalinity in PRF-treated wounds compared with controls, suggesting improved wound microenvironment **Conclusions**: Autologous PRF accelerated pedicle graft healing in goats by enhancing collagen deposition and optimizing wound pH. These findings highlight the potential of PRF as an effective biological adjunct in reconstructive surgery

Citation: Ghadban, A. A. A. Effect of Autologous Platelet-Rich Fibrin on Pedicle Skin Graft Healing in Goats: Clinical and Biochemical Evaluation. Central Asian Journal of Medical and Natural Science 2026, 7(1), 568-579.

Received: 08th Oct 2025
Revised: 15th Nov 2025
Accepted: 24th Dec 2025
Published: 21th Jan 2026

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Keywords: Autologous Platelet-Rich Fibrin (PRF), Pedicle Skin Graft Healing, Skin Graft Biochemical Evaluation, Hydroxyproline Content, Wound Healing in Goats, Platelet-Rich Fibrin in Wound Healing, Clinical Evaluation of Skin Grafts, Skin Wound pH Levels, Collagen Synthesis in Wound Healing, Avulsion Injuries Treatment, Inflammatory Phase of Wound Healing, Platelet Concentrate in Surgery, Biochemical Markers for Wound Healing, Reconstructive Surgery in Animals, Healing of Experimental Wounds.

1. Introduction

Avulsion injuries, though uncommon, often result in extensive tissue damage. They involve the abrupt separation of the skin and subcutaneous tissues from the underlying structures, typically caused by high-energy shearing forces such as those occurring in vehicular or industrial accidents, depending on the severity or nature of the trauma as well as the magnitude and duration of the energy impact [1] .

Pedicle flaps represent a reconstructive technique in which a segment of skin and subcutaneous tissue is mobilized while maintaining attachment to its original blood and nerve supply. In contrast, free skin grafts are completely detached and depend entirely on revascularization from the recipient bed. Due to their greater thickness, pedicle flaps

require a longer period for neovascular integration and are more susceptible to complications such as pedicle compression, kinking, or excessive tension at the base [2].

Wound healing follows a dynamic sequence of three overlapping stages: the inflammatory, proliferative, and maturation phases. During the initial inflammatory stage, necrotic tissue and contaminants are cleared as immune responses are activated at the site of injury. The proliferative phase is marked by angiogenesis, extracellular matrix deposition, and re-epithelialization, reflecting active tissue replacement. Finally, the maturation or remodeling stage involves collagen reorganization and progressive recovery of tensile strength, enabling partial restoration of the tissue's pre-injury properties.

Platelet-rich fibrin (PRF) is a second-generation autologous platelet concentrate prepared by simple centrifugation without the addition of anticoagulants or synthetic agents. Unlike earlier platelet preparations, PRF incorporates a dense fibrin matrix that entraps platelets and leukocytes, both of which contribute to tissue repair and immune defense. The resulting fibrin clot serves as a natural three-dimensional scaffold, providing a sustained release of growth factors and enhancing the wound healing cascad

In experimental models of skin wound repair, assessing both the amount and quality of newly formed collagen is crucial. As the predominant structural protein of connective tissue, collagen plays a central role in restoring tissue integrity. Effective healing depends on the balanced regulation of collagen biosynthesis, its deposition within the extracellular matrix, and the subsequent remodeling and maturation that confer tensile strength to the repaired tissue [3].

The aim of the study was to evaluate the effect of autogenic PRF on skin pedicle graft to treat experimental avulsion wounds, the evaluations were Performed include clinical and biochemical (hydroxyproline) evaluations and acidity (pH) test

2. Materials and Methods

The experiment was conducted on 15 adult female goats, aged between 7-8 months and weighted 18-20 Kg. Before Surgery, ten milliliters of blood were drawn from the jugular vein. The blood was immediately transferred to a 10-mL sterile plastic tube (PRF Tube; without anticoagulant, evacuated tube), and centrifuged at 1500 rpm for 14 min in a centrifuge (figure 1). The resultant product consists of three layers. The topmost layer consists of acellular PPP (platelet-poor plasma), PRF clot in the middle, and RBCs at the bottom of the test tube (Figure 2). The fibrin clot obtained after centrifugation is removed from the tube and the attached red blood cells scraped off from it and discarded (figure 3).

Surgery was performed under heavy sedation and complete aseptic conditions, 2 skin marks (2×2 cm) were created on both sides of the trunk region of the animal. Two full thickness of the marked skin is cut carefully (figure 4, a). Advancement or sliding flap (2×6 cm) are harvested parallel to the lines of least tension and are then slid over the adjacent wound (figure 4, b). These wounds are allocated into 2 groups, the 1st one as the control group (without local treatment) and the second group treated with autogenic platelet-rich fibrin as PRF-treated groups (figure 4, c). The 2 groups are represented in each goat. The edges of the wounds were closed with a simple interrupted pattern by 2-0 nylon monofilament suture. Occlusive dressing was used to protect the grafts from dryness and infection.

Clinically wound assessment post-surgery was performed as the following considerations: The general health condition of the animal, Color of the skin wound, Swelling, and exudates.

The exudates scores were estimated as non (1), light (2), moderate (3), and heavy (4). while swelling scores classified into non 0, mild 1, and obvious 3 (Nikkhah et al. 2013).

The measurement of hydroxyproline allowed for the analysis of collagen and cross-links. As previously mentioned, samples were collected, and their hydroxyproline concentration was measured using a modified spectrophotometer technique.

At 7, 14, and 21 days after surgery, collected samples from the control, PRF, and normal skin groups.

The samples were hydrolyzed in 6 molar HCl for 14–16 hours at 105°C, and the hydroxyproline was then oxidized by chloramine. Then, T. Ehrlich's reagent was used, and incubation at 60°C was required to produce a chromophore. The hydroxyproline product in the alkaline medium was extracted into toluene and subsequently into the acid phase to eliminate interfering chromophores. The hydroxyproline content was determined using a calibration curve based on standard solutions run in the same manner as samples, and the acid phase's absorbance was measured at 543 nm. In parallel with sampling for hydroxyproline analysis, 50–100 mg of each sample was put on a plate and dried in an oven at 100°C for three hours to calculate the percentage of dry matter (DM) in each sample. The last step was to express the hydroxyproline content of skin samples in ugr/g DM [4].

The level of acidity was detected at the period 5th,7th,14thand 21th days post-surgery. The procedure was carried out by spraying normal saline at the site of skin (treated, control, and normal skin), then the strips of PH detector were put on the skin surface, the color of the PH strip turn to different colors according to the acidity of the skin sites as we mentioned before. The result colors were compared with a standard color leaflet to detect the number of PH levels (Figure 5).

Results were expressed as mean values standard errors. Data were statistically analyzed by independent samples T-test using a statistical software program (SPSS for windows version 22, USA) Differences were considered significant at ($P \leq 0.05$).

Figure 1: collection the venous blood from the jugular vein

Figure 2a: centrifugation the blood sample with 1500 round per 14 mints

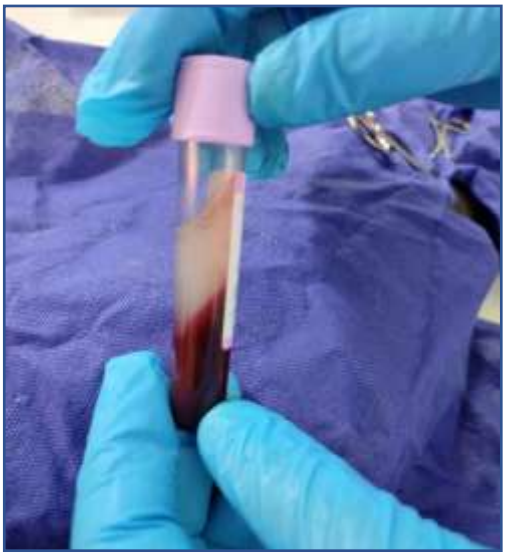

Figure 2b: the accumulation of PRF inside tube after centrifugation

Figure 3: the PRF glue was isolated from the blood

Figure 4a: skin pedicle flap was done by 2 parallel incisions

Figure 4b: Suturing the pedicle flap was complete with simple interrupted suture pattern

Figure 4c: the site of surgery was covered by wound dressing

Figure 5: measuring the level of acidity by using PH test paper

3. Results and Discussion

Clinical evaluations

There was no change in the animal's appetite after the surgery. The temperature in all animals increased by one degree on the day of the surgery and returned to normal

On the first postoperative day, fluid exudation was at the site of the wound in the treated group, while in the control group, the exudation in small amount was observed. On the second, third, and fourth post-surgery, it was observed that there were a small number of exudates and that exudation gradually disappeared in the treated wounds. However, there was disappearance of fluid exudates in the control wounds at the 3rd day (figure 5, table 1).

Swelling was observed in the patched skin area on the first and second day in the treated group of wounds and then the swelling disappeared within the next three days. However, in the control group, the swelling was greater and remained for a longer period, as it continued until the seventh day (figure 6, table 2).

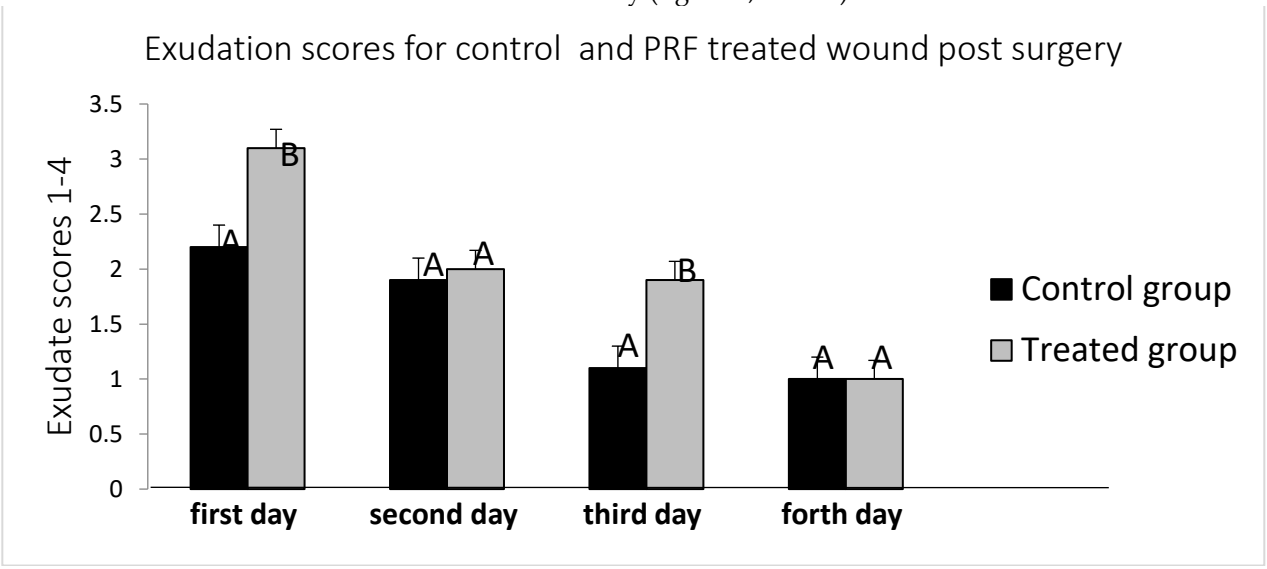

Figure 6: clinical study showed the exudates scores for skin grafts of Control and PRF treated groups wounds during (1, 2, 3 and 4 days post-surgery). ^{ABC} Different letters among groups indicates significant differences ($P< 0.05$).

Table 1. Clinical study showed the exudates scores for skin grafts of Control and PRF treated groups wounds (1, 2, 3 and 4 days post-surgery) (means and standard errors).

Groups	1st day	2nd day	3rd day	4th
Control	2.2 ± 0.2^{A}	1.9 ± 0.17^{A}	1.1 ± 0.1^{A}	1.0 ± 0.0^{A}
PRF	3.1 ± 0.17^{B}	2.0 ± 0.14^{B}	1.9 ± 0.1^{B}	1.0 ± 0.0^{A}

ABC Different letters within each column indicates significant differences ($P<0.05$).

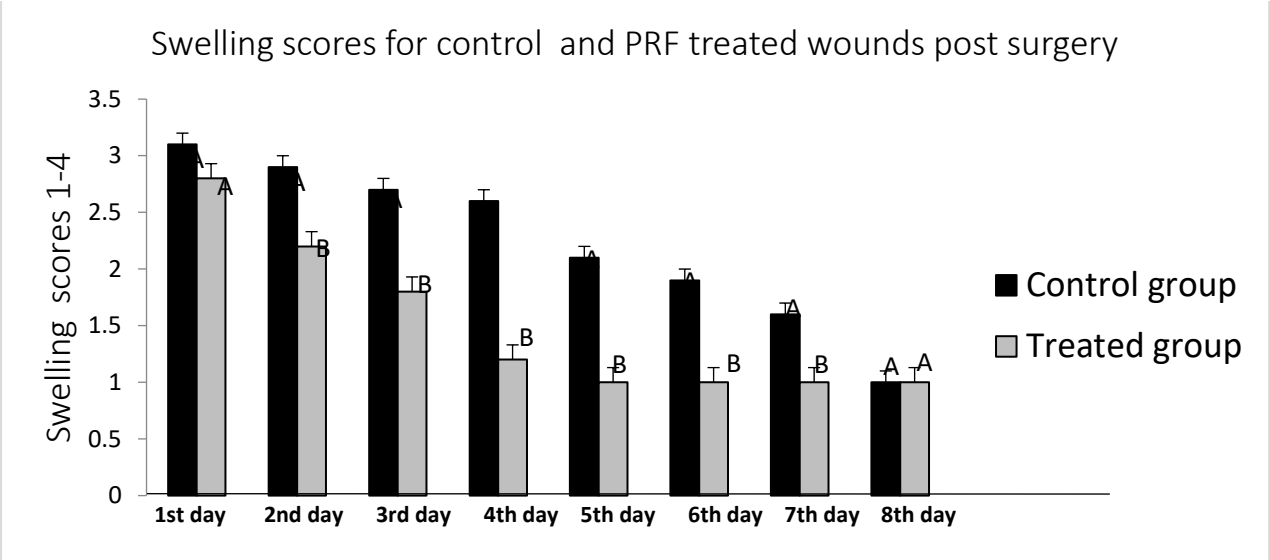

Figure 6. Clinical study showed the Swelling scores for skin grafts of Control and PRF treated groups (1-8 days post-surgery). ABC Different letters among groups indicates significant differences (P< 0.05).

Table 1: clinical study showed the swelling scores for skin grafts of Control and PRF treated groups (1-8 days post-surgery) (means and standard errors).

Group	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day	8th day
Control	3.1± 0.1A	2.9± 0.1A	2.7± 0.15 A	2.6± 0.16 A	2.1 ± 0.1 A	1.9± 0.17 A	1.6± 0.16 A	1.0 ± 0.0 A
PRF	2.8± 0.13 A	2.2± 0.13 B	1.8± 0.13 B	1.2± 0.13 B	1.0 ± 0.0 B	1.0± 0.0B	1.0± 0.0B	1.0 ± 0.0 A

ABC Different letters within each column indicates significant differences (P<0.05).

Hydroxyproline evaluation:

The results of hydroxyproline content were summarized on table 2 figure 6.

The hydroxyproline content was significantly higher on days 7 and 14 after grafting in the control group and treated group than in normal group.

On days 21 post-surgery, the hydroxyproline content showed no significant difference between treated, control and normal groups, but there was slight decrease in control group.

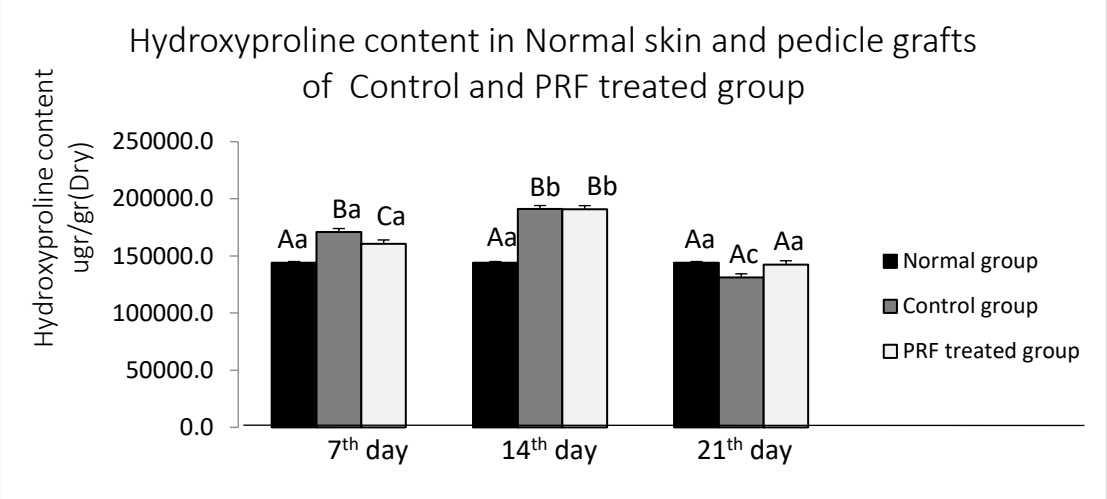

Figure 6: Biochemical study showed the hydroxyproline content for normal skin and skin grafts of Control and PRF treated groups during different periods post grafting (7, 14 and 21 days post-surgery). ^{ABC} Different letters among groups indicates significant differences ($P< 0.05$). abc Different letters within group indicates significant differences ($P<0.05$).

Table 1: study of hydroxyproline content for normal skin and skin grafts of Control and PRF treated groups during different periods post grafting (7, 14 and 21 days post-surgery) (means and standard errors).

Groups	7th day	14th day	21th day
Normal	144130.4±1014.5^{Aa}	144130.4±1014.5^{Aa}	144130.4±1014.5^{Aa}
Control	170961.3±3057.9^{Ba}	191101.8±5229.5^{Bb}	131302.2±6481.9^{Ac}
PRF	160707.6±3286.7^{Ca}	190775.2±2883.7^{Bb}	142514.0±7283.2^{Aa}

ABC Different letters within each column indicates significant differences ($P<0.05$). abc Different letters within each row indicates significant differences ($P<0.05$).

PH levels evaluation

On the fifth, seventh, and fourteenth days after surgery, the acidity results showed a significant difference between the three groups (normal, control, and PRF-treated groups) (figure 8 table 3). The result of the PH level in the treated group was significantly higher as compared to the other groups. In addition, the control group was significantly increased more than normal. However, on the twenty-first day after surgery, the results showed that there was no significant difference between the control and normal groups, but there was a significant increase in the pH level in the treated group.

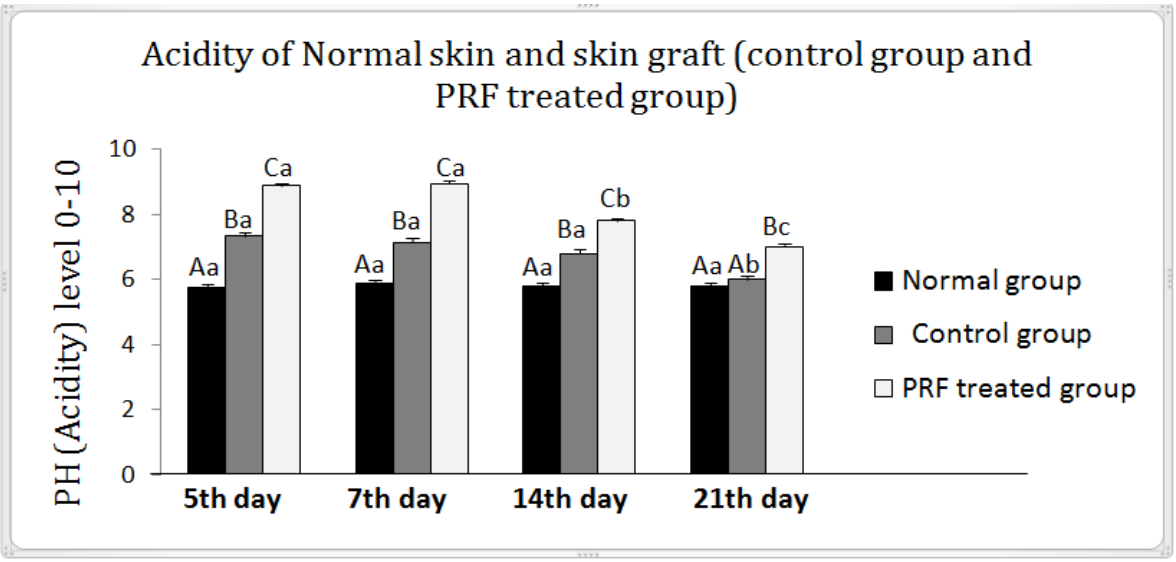

Figure 8: the clinical study showed the PH levels (Acidity) for Normal skin and skin grafts of Control and PRF treated groups during different periods post grafting (5, 7, 14 and 21 days post-surgery). ABC Different letters among groups indicate significant differences (P< 0.05). abc Different letters within the group indicate significant differences (P<0.05).

Table 3: levels of PH (Acidity) for Normal skin and skin grafts of Control and PRF treated groups during different periods post grafting (5, 7, 14 and 21 days post-surgery) (means and standard errors) .

Groups	5th day	7th day	14th day	21th day
Normal	5.73 ± 0.11^{Aa}	5.86 ± 0.09^{Aa}	5.8 ± 0.13^{Aa}	5.8 ± 0.2^{Aa}
Control	7.33 ± 0.12^{Ba}	7.13 ± 0.09^{Ba}	6.8 ± 0.13^{Ba}	06 ± 0.1^{Ab}
PRF	8.86 ± 0.09^{Ca}	8.93 ± 0.06^{Ca}	7.8 ± 0.13^{Cb}	07 ± 0.1^{Bc}

ABC Different letters within each column indicate significant differences (P<0.05). abc Different letters within each row indicate significantly

In the same group within the different periods of taking pH measurements, the results of the control group showed no significant differences in 5, 7, and 14 days after surgery. But it decreased at 21th day.

However, in the treated group, there is no significant difference in PH levels during periods 5, and 7 days after the surgery, but there were significant decreases in periods 14 and 21 days after the surgery.

Discussion:

The importance of dealing with wounds is due to the possibility of infection of the wound due to the large size of the avulsion part from the skin, usually caused by attacks of predators, injuries to industrial equipment, or car accidents.

The aim of the study was clinical and biochemical (hydroxyproline content) evaluation of skin pedicle grafts treated with autogenic PRF .

Clinical examination showed the amount of wound exudation in the treated group was in a significant increase compared to the control group. However, these exudates are showed in acute wounds in the normal range of inflammatory stage period. Therefore, these excessive healthy acute exudates induced by PRF promote the healing process in the treated group .

Exudates are sometimes called "wound fluid" and "wound drainage." A rupture in the skin initiates an inflammatory reaction and causes the capillaries to become more permeable. Serous fluid seeps into the wound bed and serves as the foundation for exudates, water, electrolytes, minerals, proteins, inflammatory mediators, proteases, growth factors, white blood cells, and microbes. It is a natural element of the healing process and provides a moist environment that permits epithelial cells to move over the wound. The growth agents and nutrients included in exudates are essential for wound

healing, and the wet climate also promotes autolysis (the separation of necrotic tissue from healthy tissue) .

In the treated group, the swelling disappeared within the next three post operative days. However, in the control group, the swelling was greater and remained for a longer period, as it continued until the seventh day.

From a clinical standpoint, this stage is distinguished by symptoms like redness, heat, swelling, and pain when seen from a clinical perspective. These symptoms are the direct consequence of mast cells releasing vasoactive amines and histamine-rich granules into the bloodstream. These mast cell mediators induce the vessels around the injury to become leaky, making it possible for neutrophils to migrate quickly and efficiently from the vasculature to the area of damage. As a result of the veins being leaky, fluid can flow into the region, producing swelling, which in turn causes discomfort due to pressure [5], [6] .

As we knew in the treated group, we added PRF, which is rich with inflammatory cell, growth factors and fibrin, this result in acceleration of the debridement or inflammatory stage and speeding up proliferation stage, this result agreed with [7]

Granulation tissue formation characterizes the period of new tissue creation. Intense fibroblast proliferation and migration are necessary for synthesizing new extracellular matrix in the region of injured tissue. Once in the wounded tissue region, fibroblasts generate new matrix elements such as proteoglycans, glycosaminoglycans, and collagen, which are deposited in the damaged area to replace the original temporary matrix, which was initially composed of fibrin.

The primary structural component of granulation tissue is collagen, which strengthens the extracellular matrix. The amino acid proline is an essential component of the collagen fiber, and hydroxyproline is a biochemical marker for collagen tissue that indicates the healing process is progressing. Therefore, the hydroxyproline test is the gold standard for evaluating collagen formation. [3], [12] [11].

The hydroxyproline content was significantly higher on days 7 and 14 after grafting in the control and treated groups than in normal group .

Hydroxyproline is an uncommon amino acid present in the collagen fibers of granulation tissues. Biochemical analysis revealed increased hydroxyproline content, which is a reflection of increased cellular proliferation and therefore increased collagen synthesis, during proliferation stage [8]

On days 21 post-surgery, the hydroxyproline content showed no significant difference between treated, control and normal groups, but there were slight decrease in control group. This result comes from action of Platelet-derived growth factors and TGF- which have been identified in PRF [15], [16]

Platelet derived growth factors increase cell proliferation and migration, and collagen production, and it shown to enhance regeneration of the graft [9]. In addition, the TGF can promote mechanical strength in healing skin graft by regulating collagen I and III synthesis, cross-link formation, and matrix remodeling [10], [13], [14].

The pH value indicates the concentration of H+ ions in solution inside the interstitial milieu of wounds. It ranges from 0 and 14. The optimal pH value for chemical reactions is determined by endogenous and external variables, such as the surrounding temperature. The pH value is a significant predictor of the metabolism during wound healing and, thus, a critical parameter for treatments in wound care [17], [18].

On the fifth, seventh, and fourteenth days after surgery, the PH level in the treated group was significantly higher as compared to the other groups. In addition, the control group was significantly increased more than normal. However, on the twenty-first day after surgery, there was no significant difference between the control and normal groups, but there was a significant increase in the pH level in the treated group [19] .

The results showed that the PRF was observed to be alkaline and alkalinity increased on day 5. Hence, it may be beneficial in wound healing for the cases where a large area of tissue is removed, and the tissue needs more O2 consumed for metabolism and regeneration then the wound pH lowers significantly. The PRF may increase pH and may

restore normalcy. This result may disagree with [20], they considered the APRF have acidic PH through an invitro study [20] .

Inflammation, proliferation, and maturation are often referred to as the three phases of wound healing. The blood coagulates and creates a temporary plug in the first minutes or hours after damage, the inflammatory phase's early stage. Since blood has a pH of around 7.4, the wound's pH would be extremely near to this level. However, as wound healing occurs, the pH of the wound changes. At this point, the wound has healed and the pH has returned to normal. The proliferation and migration of various cell types are influenced by (local) pH in this wound healing scenario. Keratinocytes and fibroblasts, two kinds of wound healing cells, proliferate best at an acidic pH range of 7.2 to 8.3. The matrix metalloproteinases of the enzyme are essential for the health of both kinds of cells. Degrading zinc-dependent enzymes play an important role in cell migration by destroying the extracellular matrix in front of migratory cells. In vivo, these enzymes have pH optimums of around [21], [22]

In 2017, Bennison et al. stated that the wounds characteristically have a neutral to alkaline pH existing in the pH range of 6.5 to 8.5 while chronic wounds exist at a range of 7.2 to 8.9. however, our results showed that the PH of the treated group reach 8.9 on day 5 post-surgery but the clinical evaluations of these wounds expose no signs of a chronic wound. we assumed the inflammatory stage was accelerated by PRF treatment and the proliferative stage was already begun [23], [24], [25].

In 2016, Jones found that the pH range between 7.2 and 8.3 is ideal for keratinocyte and fibroblast growth, which documented this range. Unlike dermal fibroblasts, epidermal keratinocytes can withstand a significantly broader pH range. Furthermore, epidermal keratinocytes demonstrate the best migration from ex vivo skin explants at a pH of 8.55. This is consistent with previous research that found a higher pH to be beneficial for the survival of skin grafts after burn injuries. Keratinocyte growth, viability, and migration are hampered in an environment with a low pH. showed that a low pH hinders multilayer epidermal regeneration using keratinocyte/fibroblast 3D skin constructions. Greatly slowed migration at pH 6.5 compared to pH 7.4, and this difference was seen between the two. This suggests that keratinocytes may not be recruited in sufficient numbers owing to a decreased pH near the wound borders. As a result, the epidermal barrier cannot be repaired [26], [27], [28], [29].

Blatt et al. proved in 2022 that PRF has an antibacterial impact against bacteria in anaerobic environments, such as a dental root canal or a local pyoderma gangrenosum. It illustrates PRF's ability to modify pH levels even in anaerobic environments. By these findings, the current research demonstrated that the average pH level of PRF matrices began at 8.9, but decreased throughout time, demonstrating the ability of PRF to optimize pH levels at wound healing sites [30], [31].

Within the different periods of taking pH measurements, the control group showed no significant differences in 5, 7, and 14 days after surgery, lastly, it decreased in 21th day. However, in the treated group, there was a significant decrease in periods 14 and 21 days after the surgery.

Bennison et al. demonstrate that open wounds have a neutral to alkaline pH range of 6.5 to 8.5, but chronic wounds have a pH range of 7.2 to 8.9 In addition, Jones et al. (2015) supported that, as wounds proceed through the phases of healing, a change toward an acidic pH takes place [32], [33]]], [34], [35], [36].

4. Conclusion

1. PRF could promote the regeneration and maturing of the wound and enhance hydroxyproline content in skin pedicle graft .

2. The improvement of biochemical properties for the PRF treated group and relative magnitude of these results compared with those of control group suggest that the PRF group had the potential for more rapid return to normal function, and indicate the improvements associated with introducing PRF into the repair skin pedicle graft.

3. The PRF was observed to be alkaline and it may increase the pH level in the pedicle grafts and restore a normal environment in the wound.

Acknowledgment: All of the volunteers who helped us complete and publish this research are acknowledged. We are grateful for their efforts .

Conflict of interest: According to the authors of the article, no conflicts related to interests arose during the drafting phase.

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